Serial No. 09/721,550

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Norbert Reich	Examiner:	Taylor, J.
Serial No.	09/721, 550	Group Art Unit:	1655
Filed:	November 22, 2000	Docket No.	510015-234
Title:	POLYMER ARRAY ON A SOLID SUBSTRATE		

CERTIFICATE UNDER 37 CFR 1.8
I hereby certify that this correspondence and identified enclosures are being deposited with the United States Postal Service, first class mail, postage prepaid, under 37 C.F.R. 1.8 on the date indicated, and is addressed to the Commissioner for Patents, BOX: Non-Fee Amendment, Washington, D.C. 20231 on January XX, 2002.

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Valerie Mata

DECLARATION OF DR. STANLEY NELSON

BOX: Non-Fee Amendment
Assistant Commissioner for Patents
Washington, D.C. 20231

I, Dr. Stanley Nelson, hereby declare as follows:

1. I am a professor in the Department of Human Genetics at University of California, Los Angeles School of Medicine at 5506B Gonda Center, UCLA, Los Angeles, CA 90095. I have personal knowledge of the facts recited in this declaration and could testify competently thereto.

2. I have been employed by University of California, Los Angeles for approximately 8 years, and my title is Associate Professor of Human Genetics. I received my Bachelor of Science degree in Physics from University of Michigan in 1982, and my M.D. Degree from Duke University in 1987. In addition to my employment at University of California, Los Angeles, I have been working in the field of microarrays since about 1991 and recently in collaboration with EpigenX of Santa Barbara. A true and correct copy of my resume is attached hereto as Exhibit A.

3. I have been asked by Oppenheimer, Wolff & Donnelly, patent counsel for the Applicant, Reich, to review the patent application by Reich, the pending claims by Reich and U.S. Patent No. 6,100,030 to McCasky et al. I have thoroughly reviewed these documents and understand them.

4. In general, the methods described in the patent application by Reich involve: a) labeling and modifying a probe by incorporation of nucleotide analogs including 2-aminopurine; b) affixing the labeled probe on a substrate including an array; c) detecting a first level of label from the labeled probe on the substrate; d) hybridizing labeled probe to a homologous but unlabeled and unmodified target molecule in solution, e) detecting a second level of label from the labeled probe on the substrate, and f) identifying a probe/target hybridized pair by comparing a first and second levels of label from the labeled probe.

5. U.S. Patent No. 6,100,030, (McCasky) describes a "[m]ethods of genoytyping amplified mixtures of DNAs, nucleic acid markers and methods of obtaining markers, kits, recombinant plants, positional cloning and integrated systems for making genotypes and assessing hybridizations (Abstract)."

6. I have been asked to give my opinion regarding statements in McCasky, column 23, lines 40-51, in particular, lines 46-48, where McCasky states

"[w]here the probe is labeled, hybridization is typically detected by quenching of the label."

7. The phrase of McCasky, column 23 in lines 46-48, "[w]here the probe is labeled, hybridization is typically detected by quenching of the label." has nothing to do with the methods claimed by Reich. The term "typical" used by McCasky at the time of the filing of the McCasky, namely, January 10, 1997 and January 9, 1998 refers to two types of fluorophore:fluorophore interactions: (1) quenching; and (2) fluorescence resonance energy transfer. Quenching as of the time of the McCasky filing would be interpreted to mean that when two fluorophore molecules are in close proximity to each other, one or both fluorophore molecules will quench. For example, if there are two fluorophore molecules: molecule 1 and 2 where molecule 1 is on the surface and excites with a short wavelength and emits with a longer wavelength. If molecule 2 is brought into close proximity with molecule 1, molecule 2 is able to absorb the energy of the molecule 1 and thus, emit an even longer wavelength. This phenomenon is otherwise called fluorescence resonance energy transfer, and is a very common technique for detecting how close two molecular interactions occur because if the two molecules are in very close proximity, one molecule will in effect quench the emission of the other molecule. For example, emission detected molecule 2 will be further to the red or longer wavelengths. Thus, in my view to one skilled in the art, McCasky is referring exactly to this type of quenching (column 23, lines 46-51). However, this is not well delineated in the McCaskey patent.

8. When comparing the disclosure of McCasky, more particularly to the statements in column 23, lines 40-51, to that of the pending patent claims of Reich, I find no teachings in McCasky that is applicable to the process of the pending claims in the Reich patent application. In some of the pending claims of Reich, labeled nucleic acid molecules are attached to the substrate and fluorescence from the

labeled nucleic acid molecules is quenched when the labeled nucleic acid molecules are hybridized to target molecules.

9. McCasky does not disclose or suggest the subject matter of the application by Reich because at the time of filing of McCasky's, the methods of detecting the labeled probe as claimed by Reich were not known in the art. These methods are not taught, disclosed or suggested in McCasky. That is, at the time of filing of McCasky, "typical" detection of labeled probe by quenching did not occur by the same methods claimed in Reich. McCasky's "typical" detection of labeled probe by quenching can only occur by means as described above (or fluorescence resonance energy transfer). The quenching effect of McCasky cannot be interpreted to mean that there is specific reduction of levels of label when a labeled probe is hybridized to its homologous unlabeled target. This phenomenon is first described in the application by Reich and is set out **in some of the pending claims**.

10. Another key difference between the inventions of Reich and the disclosure of McCasky is that **in some of the pending claims** of Reich the probe is labeled or modified by incorporation of fluorescent nucleotide analogs including 2-aminopurine. It is established in the field and in the literature that various fluorescent nucleotide analogs can be incorporated into native molecules and upon binding or hybridization to their unlabeled and unmodified homologues (or targets in solution) will have reduced levels of fluorescence or "quenching". This same term, "quenching," does not have the same meaning when used in McCasky in column 23, lines 40-51. Further, McCasky does not describe incorporation of a fluorescent nucleotide into a native molecule, nor does McCasky describe that the targets in solution are unlabeled or unmodified.

11. Further, McCasky relies on the technology and methods previously described by Fodor et al., (1991) and manufactured by Affymetrix of Santa Clara, California. Fodor and Affymetrix describe methods whereby targets in solution are labeled and contacted with unlabeled probes on a substrate. These methods are the exact opposite of the methods claimed in the application by Reich.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements or the like may jeopardize the validity of the application or any patent issuing thereon.

Stanley Nelson, M.D. Date Feb 1, 2002